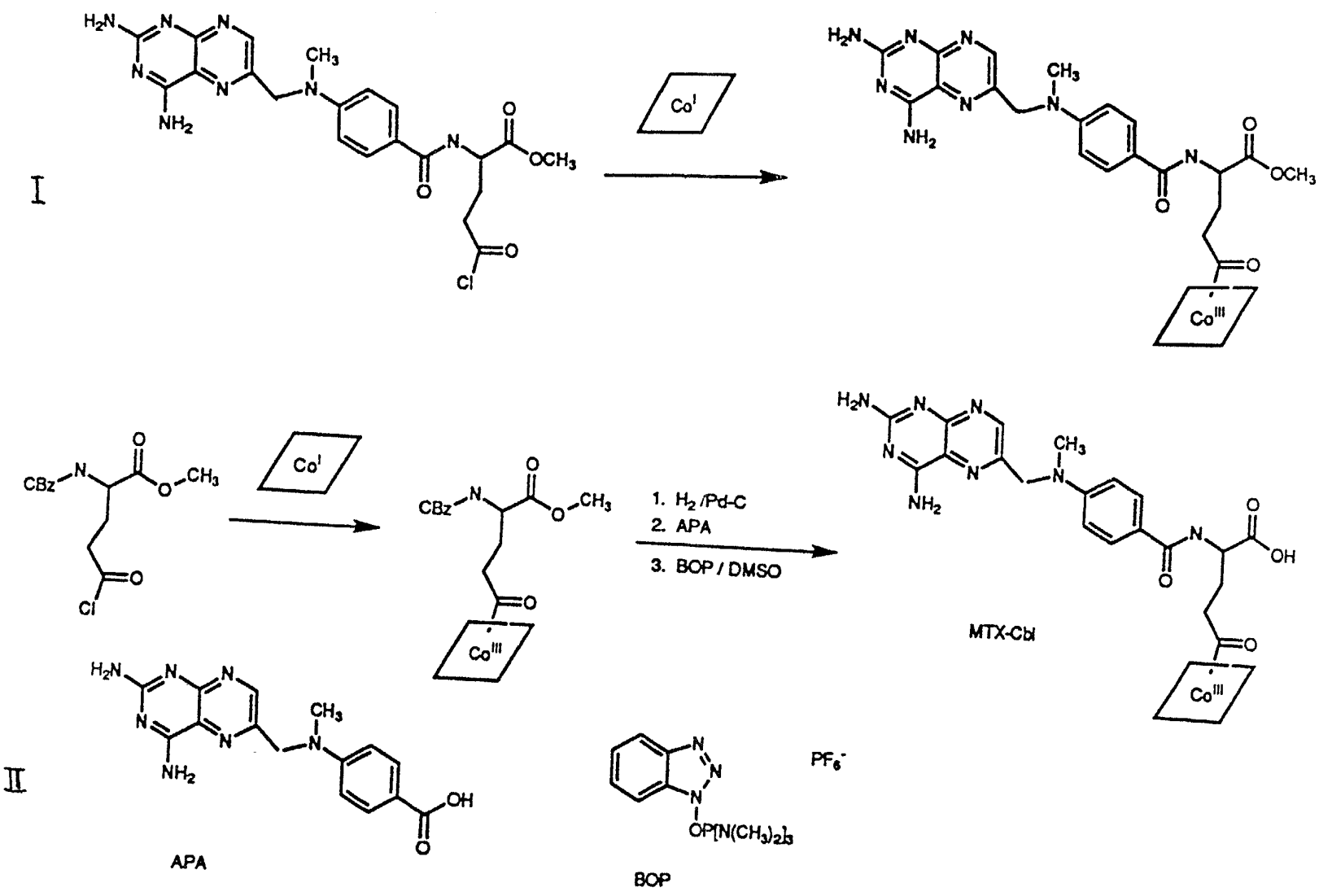
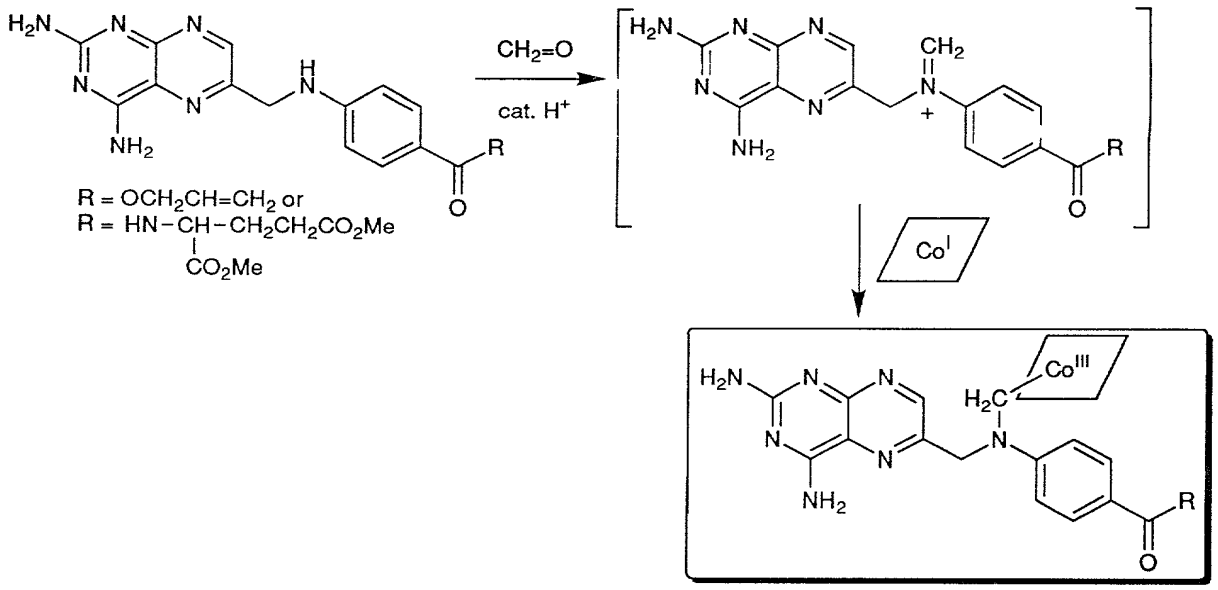
resulting aqueous solution is diluted with an equal volume of H_2O and loaded onto a Dowex AG-50-X2 (200-400 mesh) cation exchange column. The column is washed sequentially with H_2O and 0.1 M NaOAc, pH 6.4. Fractions containing drug-cob(III)alamins appear red and are collected appropriately. Unreacted hydroxocob(III)alamin is retained on the column. Combined fractions of drug-cob(III)alamin are extracted with phenol and concentrated by rotary evaporation. Drug-cob(III)alamins can often be crystallized by the addition of acetone to a concentrated aqueous solution. Characterization of the alkyl-, acyl-, or aryl-cobalamin conjugates is by NMR, mass spectrometry (FAB, Cl, or electrospray), and IR methods.

A methotrexate-containing bioconjugate can be synthesized by the following methods.

In method one utilizing the above procedure, methotrexate (MTX) is converted to its corresponding acyl chloride and reacted with cobalamin and/or Co(III)[SALEN] and/or other disclosed organocobalt complexes to yield methotrexate-cobalamin and methotrexate-Co(III)[SALEN] according to the following reaction scheme I. In the alternative method two, the C-Co bond is first formed from an acyl chloride having a protected amino group. The amino group is then deprotected, followed by formation of the amide bond to an aminobenzoylpterin according to the following reaction scheme II.


I
Co'
Co'''
II
CBz
1. H2/Pd-C
2. APA
3. BOP / DMSO
MTX-Cbl
APA
BOP
PF6-

An aminopterin-containing bioconjugate can be synthesized by the following method. The des-methyl derivative of methotrexate (aminopterin) is coupled to cobalt as shown by the following reaction formula, in which the iminium ion is either reacted with Co(I) directly, or the iminium ion is converted to the aminonitrile and then slowly unmasked to reveal the iminium cation.



A topotecan-containing bioconjugate can be synthesized by the following method. The cytotoxic activity of topotecan (TPT) or camptothecin (CPT) arises from their ability to freeze topoisomerase I-DNA "cleavable complexes." (Pommier et al., 1995) Since some tumor types display greatly elevated levels of topo I (Giovanella et al., 1989), topoisomerase poisons of this type are likely to have a higher therapeutic index in the treatment of those cancers. However, treatment with camptothecin derivatives could be made more general if used in conjunction with the targeted delivery approach.

Topotecan is conjugated to cobalamin, Co[SALEN] and other organocobalt complexes according to the following reaction schemes. Camptothecin is conjugated in a similar manner. Preparation of **10a** and **10b** involves similar chemistry to that discussed above for **8a,b**. Selective generation of the phenyl chloroformate (**25**) of topotecan (**5**) and acylation of Co(I) gives **10a**. Exposure of **25** to **18** or treatment of **5** with the previously discussed chloroformate **19** furnishes **10b**. Conjugates **10c,d** will require somewhat longer routes, as they cannot be prepared directly from **5**. However, the established synthetic route for conversion of the natural